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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MORGAN, LEWIS & BOCKIUS, LLP
ONE MARKET SPEAR STREET TOWER
SAN FRANCISCO, CA 94105

EXAMINER	
GODDARD, LAURA B	
ART UNIT	PAPER NUMBER
1642	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,712	COLLAND ET AL.	
	Examiner	Art Unit	
	LAURA B. GODDARD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14-55* is/are pending in the application.

4a) Of the above claim(s) *1-12 and 14-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/13/06, 3/3/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Election filed June 24, 2008 in response to the Office Action of March 25, 2008 is acknowledged and has been entered. Applicants elected Group VII (claims 54 and 55) without traverse and the species of target gene "GPR49" and inhibitor compound that inhibits proteins and peptides as recited in claim 28.

Claims 1-12, 14-55 are pending. Claims 1-12 and 14-53 are withdrawn from further consideration by the examiner under 35 CFR 1.142(b) as being drawn to non-elected inventions. Claims 54 and 55 are currently under prosecution.

NOTE: Claim 54 recites claims 28 and 33 which are claims withdrawn as being drawn to a non-elected invention.

Specification

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a)(1) and (a)(2). Specifically:

(A) there are no SEQ ID NOs identified with the sequences disclosed in Figures 15, 18, 19, 21A, and 23 and on page 36 (GUS oligonucleotides); and

(B) there is no sequence listing provided for the instant application.

Applicant must correct these informalities (See MPEP 2422).

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, for example on pages 7, 23, and 29. Applicant

is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

4. The disclosure is objected to because of the following informalities: The specification does not provide section headings. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use:

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification should include section headings, for example: TITLE OF THE INVENTION, CROSS-REFERENCE TO RELATED APPLICATIONS, FIELD OF THE INVENTION, BACKGROUND OF THE INVENTION, SUMMARY OF THE INVENTION, BRIEF DESCRIPTION OF THE DRAWING(S), and DETAILED DESCRIPTION OF THE INVENTION. Appropriate correction is required.

5. The specification is objected to for the following reason: The specification on page 1 should be amended to reflect the most current priority status of the present application, under a heading of "Cross-Reference to Related Applications" or "Related Applications". For example, this application is a 371 of PCT/EP03/07399 filed 07/08/2003, which is a CIP of Application No. 10/197,619 filed 7/16/2002.

Drawings

6. The drawings are objected to because several Figures have a title with a different Figure number or letter that contradicts the actual Figure number or letter. **For**

example, Figure 15A states at the top "Figure 1" and Figure 21C states "B" at the top. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 54 and 55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method for the development of a therapeutic inhibitor compound as set forth in claim 28 or 33, the method comprising: (a) identifying one or more genes regulated by TCF/β-catenin in colon carcinoma cells by using microarray technologies; (b) validating one or more of the identified genes as one or more potential

target genes for the therapeutic compound by one or more methods selected from the group consisting of:

(i) confirming the identified gene by Northern Blot analysis in colon carcinoma cell-lines;

(ii) determining the expression profile of the identified gene in human colorectal tumors and normal tissue; and

(iii) determining the functional importance of the identified target gene for colorectal cancer;

(c) producing the expression product of the target gene; and (d) using the expression product of the target gene for the production or design of the therapeutic compound (claim 54), the method of claim 54, wherein the target gene identified in step (a) is G protein-coupled receptor 49 (GPR49) (claim 55).

The specification discloses that TCF/β-catenin signaling (also known as WNT signaling) is deregulated in colon carcinoma cells and that the resulting inappropriate expression of target genes is considered to promote carcinogenesis. The specification contemplates that the identification of the target genes of the TCF/β-catenin signaling pathway provides the opportunity to develop therapeutic compounds or therapies that restore or neutralize the inappropriate expression of these genes when TCF/β-catenin signaling is deregulated. The specification contemplates that by normalizing the expression pattern of one or more of the target genes, the drugs can halt or reverse the further development of existing cancer cells, such as colon carcinoma cells, thus restoring the normal cycle of events (p. 4, lines 1-19).

The specification discloses genes, including GPR49, in Table 1, whose mRNA expression is down-regulated after a colon carcinoma cell line (LS174T) is transfected to express a dominant-negative form of TCF-4 (dnTCF4) (see also Figure 2A). Example 3 discloses RT-PCR of GPR49 to determine expression levels in colon cancer cell lines:HT29, LS174T, HCT116, and SW480. GPR49 mRNA expression was detected in HT29, LS174T, and SW480, but not in HCT116 cell lines (Figures 8A and 8B). It is noted that no expression levels in normal control colon cells were determined, nor in primary colon cancer or normal tissues. No protein expression was determined, nor the protein's role or association with carcinogenesis in colon cancer.

The specification contemplates establishing the contribution of specific target genes to colon cancer by dominant-negative expression of target genes with mutations to suppress function of their endogenous counterparts in colon cancer cell lines, anti-sense/RNAi approaches, and generation of mice deficient for target gene expression in intestinal tissues using a combination of standard loxP knock-out technologies and intestine-specific Cre mouse strains, or generation of transgenic mice expressing dominant-negative target genes, in efforts to determine whether loss of target gene function *in vivo* has any adverse effect on colorectal polyp formation (p. 30-31). The specification further contemplates that many of the validated TCF/β-catenin target genes will be more highly expressed on colon carcinoma tissues than healthy tissues and some encode cancer-specific proteins, making these excellent targets against which to develop colon cancer therapeutics (p. 31-32).

Post-filing art (McClanahan et al, Cancer Biology & Therapy, April 2006, 5:419-426) teaches that GPR49 mRNA and protein expression are increased in primary colon tumor tissues as compared to normal colon tissues (abstract; Figures 2A, 2B, 3A). McClanahan et al teach the ligand and functional role of GPR49 are unknown and that increased GPR49 expression in tumor cells suggests a correlation of GPR49 with tumorigenesis (p. 424, col. 1 and 2). McClanahan et al further teach that some cell lines used in their study overexpress GPR49 but do not have activating β-catenin mutations, suggesting that β-catenin mutation does not correlate with GPR49 upregulation (p. 424, col. 1, last sentence).

One cannot extrapolate the disclosure of the specification to the enablement of the claims because the specification does not provide guidance or examples of developing a compound that will predictably function as a therapeutic inhibitor, particularly for inhibiting GPR49 protein. The specification discloses that GPR49 mRNA expression is increased in some colon cancer cell lines, but discloses nothing about GPR49 protein expression in primary colon cancer or normal tissue, does not provide a nexus between inhibition of GPR49 protein and therapeutics, and does not provide a nexus between any compounds developed using the claimed method steps predictably functioning as a therapeutic inhibitor. Although the post-filing art (McClanahan et al above) teaches increased GPR49 protein expression as correlated with colon cancer, the art does not provide a nexus between inhibition of GPR49 protein and therapy, or a nexus between the claimed methods steps and a compound that predictably functions as a therapeutic inhibitor. Further, the art teaches that disrupting the β-catenin pathway

is not correlated with GPR49 upregulation, which is a method taught in the specification to identify target genes for development of a therapeutic inhibitor.

Further, the claims are broadly drawn to "using microarray technologies" to identify one or more genes regulated by TCF/β-catenin in colon carcinoma cells and do not recite actual method steps that would allow one of skill in the art to predictably identify a gene regulated by the TCF/β-catenin pathway. Although the specification discloses transfecting cell culture to express dominant-negative TCF, measuring gene mRNA expression levels, and identifying genes that are down-regulated in mRNA expression, and although the claims are read in light of the specification, limitations recited in the specification are not read into the claims. Further, the use of cell culture for identification of genes regulated in cell culture (part (a) of claim 54) and the confirmation of the gene in Northern Blot analysis in cell culture (part ii), would not allow one of skill in the art to develop a compound that would predictably function as a therapeutic inhibitor *in vivo* as contemplated because those of skill in the art recognize that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation

in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, “petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Give the teaching of the art, one of skill in the art could not predictably extrapolate gene expression profiles or dnTNF transfection studies from cell culture to that of the development of compounds that would predictably function to inhibit proteins expressed *in vivo* therapeutically.

Further, those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo*

environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Zips et al. (2005, In Vivo, 19:1-7) teach "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro*, a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularization, perfusion and, thereby drug access to the tumor cells are not evenly distributed and this fact 'consists' an important source of heterogeneity in tumor response to drugs that does not exist *in vitro*. In the case of the instant specification, even if a gene is identified in colon cancer cell lines and confirmed to be expressed in colon cancer cell lines, given the teaching of the art above, one of skill in the art could not reasonably extrapolate that the expression product of this gene (part c and d of claim 54) would produce a compound that predictably functions as a therapeutic inhibitor *in vivo* as contemplated and claimed.

Given, the post-filing art teaches the function of GPR49 is unknown, and the instant specification discloses the function is unknown (p. 41, lines 20-21), one of skill in the art would not know how to validate the identified gene as a potential target gene for the therapeutic compound by determining the functional importance of the identified target gene for colorectal cancer (part iii of claim 54). No nexus is provided between the function of GPR49 and the developed compound predictably functioning as a therapeutic inhibitor.

Finally, the claims do not recite actual method steps for "using the expression product of the target gene for the production or design of the therapeutic compound" (part d of claim 54), therefore, one of skill in the art would know what steps to accomplish to make a compound from the expression product that would predictably function as a therapeutic inhibitor. Although the specification contemplates making antibodies, small molecules, antisense, RNAi and other compounds as candidate therapeutic compounds (p. 32-38), and although the claims are read in light of the specification, limitations recited in the specification are not read into the claims. Further, the specification does not provide a nexus between the identification of target genes as claimed and the use of the expression product of the genes resulting in the production of any compound predictably functioning as a therapeutic inhibitor.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling." Given little is known about GPR49 function or the function of GPR49

protein inhibitors as therapeutics *in vivo*, one of skill in the art would be subject to a high quantity of experimentation and be forced into undue experimentation to practice the claimed invention.

MPEP 2164.03 states: The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. Given the state of the art, one of skill in the art would not extrapolate the results of the *in vitro* assays disclosed in the specification to the enablement of the claimed method to develop a compound that would function predictably as a therapeutic inhibitor.

Therefore, in view of the state of the art, the quantity of experimentation necessary, the breadth of the claims, lack of guidance in the specification, and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

8. **Conclusion:** No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura B Goddard/
Examiner, Art Unit 1642